

CORONARY ARTERY DISEASES IN IRAQI WOMEN ANGIOGRAPHIC STUDY AND RISK FACTOR CORRELATION

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ABSTRACT

Background: Heart disease is not just a man's disease. Heart attack, stroke and other cardiovascular disease are devastating to women, too. In fact; coronary heart disease is the leading cause of death for women. Extensive clinical and statistical studies have identified several factors that increase the risk of heart disease, and heart attack. Major risks factors are those that medical research has shown significantly increase the risk of heart and blood vessel (cardiovascular) disease. The more risk factors a person has, the greater the chance that he or she will develop heart disease. Also the greater the level of each risk factor, the greater the risk.

The Aim: We study the contribution of certain variables like (the age, past history of MI, hypertension, diabetes mellitus, smoking, family history of IHD, left ventricular end diastolic pressure, ejection fraction, hyperlipidemia) with angiographic severity of coronary artery disease in Iraqi women with ischemic heart disease.

Method: In a prospective cross sectional study 292 female patient consulted Ibn-Abitar cardiac center because of ischemic symptoms underwent coronary angiography. The extent and severity of coronary atherosclerosis were assessed using Gensini severity score.

Results: Approximately 58% has a normal coronary angiogram. The remaining 41.8% have abnormal coronaries, single vessel disease constituted 47.5% while two vessel diseases constitutes 27.9% and three vessel disease constitutes 24.6%. Severe involvement as shown by the scoring constitutes 17.8%, moderate severity in 13% and mild in 11%.

Conclusions: Normal coronary angiography was so common among female patient with CAD these results suggest that, the threshold for invasive test as coronary angiography need to be raised in female patient, Diabetes mellitus was the most common variable associated with severe coronary artery disease; it increases the risk seven times as compared to those who are non-diabetic. This followed by the past history of myocardial infarction and smoking. Left ventricular end diastolic pressure more than 15 mm was associated with double the risk of severe coronary involvement.

KEYWORDS: Coronary Thrombosis, Normal Coronary, Heart Disease

INTRODUCTION

Cardiovascular disease is the principal cause of death for both men and women. Many women believe that cancer is more of a threat, but they're wrong. Nearly twice as many woman die of heart and stroke as from all forms of cancer, including breast cancer (1)

Atherosclerosis is the most frequent underlying cause of ischemic heart disease (2). Atherosclerosis is a multifactor process that develops over a life time. It is characterized by a buildup of atherosclerotic plaque within the

innermost layer of an artery wall, narrowing the vessel lumen and reducing the flow of blood to the heart (3). The serious and potentially lethal consequences of atherosclerosis such as acute coronary syndromes are usually caused by acute thrombosis on a chronic atherosclerotic plaque with a disrupted or eroded surface (4). Several studies have demonstrated that plaque composition rather than stenosis severity is a major determinant of the risk for disruption and subsequent thrombosis (5).

The American Heart Association has identified several risk factors that increase the risk of heart disease and stroke. The more risk factors a woman has, the greater the chance that she will have a heart attack or stroke. Some of these factors you can't control, such as increasing age, family health history, race and gender. But you can modify or treat other risk factor 6 with increasing age, the chances of developing heart increase as women grow older. As women approach the age of menopause, their risk of heart disease and stroke begins to rise and keeps rising with age. The loss of natural estrogen as Women increase in their age may contribute to this higher risk after menopause (6).

The incidence and prevalence of stroke are about equal for men and women. However, more than half of total stroke deaths occur in women (7). Family history, both women and men are more likely to develop heart disease or stroke if their close blood relatives have had them. Previous heart attack or stroke. (8). Tobacco smoke is the single most preventable cause of death. Women who smoke cigarettes have a much higher risk of death from heart disease or stroke. (2, 8).

Higher blood cholesterol is a major risk factor for heart disease and indirectly increases the risk of stroke. High blood pressure is a major risk factor for heart attack and the most important risk factor for stroke. About 60% of all women aged 65 to 74 have high blood pressure (8-12).

Diabetes mellitus, compared to women of the same age without diabetes have from three to seven times the risk of heart disease and heart attack and are at much greater risk of having a stroke. (7-13)

One of the most important prognostic value in predicting the outcome in ischemic heart disease is left ventricular function, those with impaired left ventricular function have a worse prognosis (25).

The Aim of the Study

In this study, we assessed angiographically the severity and extent of coronary atherosclerosis and the prevalence of certain risk factors and other parameters like ejection fraction and left ventricle end diastolic pressure, that to say the contribution of different variables in the severity of ischemic heart disease, among Iraqi female patients submitted for coronary angiography because of ischemic symptoms 2

Review of Literature

Cardiovascular disease is the most common cause of death worldwide. Since 1984 more studies about women have proved that women died more of this disease (14).

Since Tobin et al (15) reported more than a decade ago that women with abnormal nuclear exercise studies were referred far less often than men for cardiac catheterization and coronary artery bypass graft (CABG) surgery. (16,17).

In population data from Framingham and elsewhere show that women have an average of 10 to 15 years more CAD-free life expectancy than men due to a later onset of disease (13- 18).

The cause of this protection from early atherosclerosis for women is presumed to be endogenous estrogen,

although recent studies have suggested that the understanding of the link between sex hormones and cardiovascular disease is far from complete (19,20).

Framingham data demonstrated that women with CAD most commonly present with angina pectoris initially whereas men first present with myocardial infarction (MI) (21). Furthermore, in Elective presentations women tend to present with atypical forms of angina much more than men, making correct diagnosis more difficult. Even when women present with typical angina, the underlying prevalence of CAD is lower in women than in men with similar symptoms. For example, a 60-years-old Women with typical angina has approximately a 50% chance of having significant CAD whereas a 60-years-old man with the same symptoms has more than a 90% chance (22). For a man with typical angina to have a 50% chance of CAD (similar to the hypothetical 60-years-old), he would have to be in his 40s. For a women with typical angina and a probability of CAD of 90% (similar to the hypothetical 60-years-old man), she would have to be in her late 70s (22).

Thus, the same symptom complex means something different at different stages of a patient's life for both men and women. The age-related meaning for men is not relevant to women and vice versa.

Even with the aid of noninvasive tests, diagnosing CAD is more difficult in women than men. The reduced sensitivity of stress tests, which is related to the distribution of severe disease in the tested population, and the lower prevalence disease both reduce the ability of such tests to "rule in" CAD in women. Although the exercise treadmill test has often been regarded as unreliable for diagnosis in women; its prognostic value is actually equivalent to what it is in men after accounting for the lower prevalence of CAD (23). Stress imaging studies are more accurate for diagnosis of CAD in either sex but do not provide a simple solution to the greater diagnostic challenges in women. For example, in the Women's Ischemia Syndrome Evaluation (WISE) pilot study, (24), the overall sensitivity of dobutamine stress echocardiography for detection of angiographic any significant CAD in 92 symptomatic women with clinical indications for coronary angiography was only 40% with a specificity of 81%, sensitivity for detection of multivessel disease was 60%.

Importantly, the prevalence of at least 50% stenosis of a coronary artery in this group was only 27%. In this same population, the sensitivity of the exercise treadmill tests ST segment response was 25% with a specificity of 80%. With such low test accuracy for detection of CAD, it is virtually impossible to reach a high level diagnostic certainty about the presence or severity of significant CAD (25). Consequently, the different referral patterns for noninvasive testing between men and women 3

Could reflect an inappropriate physician bias and could rather seem much more likely to reflect genuine confusion about the optimal testing strategy to use.

Few studies of sex bias have been able to examine subjective physician decision making directly.

Furthermore, although women were referred for catheterization less often than men in this study (18% vs 27%), the difference was completely accounted for by differences in the pretest probability of CAD (27).

In a study of patients referred for cardiac catheterization from 1969 to 1984, 46% of men and 44% of women with significant CAD were referred for CABG surgery (28). After adjusting for baseline risk of cardiac death, Bicknell and colleagues (28), found that men were almost 30% more likely to be referred for CABG surgery when the expected survival benefit from the procedure was minimal relative to medical therapy, whereas there was a trend for more women than men

to be referred for CABG surgery in the high-risk and high-benefit sub group. (29)

Acute presentations of CAD herald a 30-day phase of substantially increased risk of mortality and morbidity; therefore sex-based differences in the management of acute coronary syndromes deserve particular scrutiny. Maynard and colleagues (30) reported the results of a major multicenter trial focused on emergency department management of acute coronary syndromes. Among 2542 patients with definite acute MI, these investigators found that use of thrombolytic therapy, cardiac catheterization, and revascularization procedures was equivalent in men and women (30). Among patients with angina without MI (a lower risk group), women underwent fewer invasive procedures. This study was adversely affected.

In the issue of the journal, Roger and colleagues (31), provide new data on the long-term outcome associated with these different patterns of care. The authors studied 1306 men and 965 women living in Olmsted County, Minnesota, who presented to an emergency department with symptoms of unstable angina between 1985 and 1992.

Patient's sex had no effect on whether they were admitted to the hospital and no effect on the use of resting echocardiography. However; men were 43% more likely to undergo stress testing and 59% more likely to undergo coronary angiography, these results complement those of Hochman and colleagues (32, 33), who found that women with acute non-ST segment elevation coronary syndromes have less significant CAD and less multivessel disease than men, despite being older and having a higher prevalence of hypertension, diabetes, and hyperlipidemia. Left ventricular function was also significantly better in women with acute coronary syndromes compared with men (33). In patients with non-ST segment elevation MI, the difference in the CAD severity was smaller and 30-day death rates and reinfarction rate were equivalent for men and women in this subgroup. (32) In contrast, among patients with unstable angina without infarction, women had a significantly lower prevalence of obstructive CAD (71% vs 86% for men, $p < 0.001$) and 35% lower adjusted risk of death or MI in the first 30 days after PCI (32, 35).

PATIENT AND METHOD

Patient Characteristics

The study was performed in Ibn al-bitar Center for Heart Disease. Two hundred and ninety two patients (all are women), underwent coronary angiography for suspected CAD between the first of April 1999 to April 2000. Each patient had a full history and clinical examination including assessment of coronary risk factors. Fasting blood sugar, total cholesterol and triglyceride. Full cardiologic assessment including CXR, ECG, Echocardiography and angiography was performed. All these tests were performed at the hospital laboratory using the standard method.

Exclusion criteria: Patients with previously known primary valvular heart disease, valvular replacement, congenital heart disease, non-ischemic cardiomyopathy, and those who had previously undergone coronary artery bypass graft surgery were excluded from the study.

ANGIOGRAPHIC ASSESSMENT

Coronary arteriography was performed by the Judkin's technique and coronary angiograms were visually analyzed by two experienced cardiologists. The degree of luminal narrowing was given in percentage from the prestenotic diameter. The right left anterior descending, circumflex and left main stem coronary arteries were considered to be normal i.e. (0%), stenosed or obstructed (25%, 50%, 75%, 90%, 99%, 100%) according to maximum obstruction observed in any projection.

The severity and extent of coronary artery stenosis was determined by Gensini score. The score were based on visual estimation of the angiograms during the frame selection process, and its severity depends on the degree of luminal narrowing, geographic importance of its location, the cumulative effects of multiple obstructions and the size quality of distal vessels (34).

DEFINITION OF CLINICAL VARIABLES

Nine variables have been studied with their relation to angiographic severity of CAD using Gensini score system.

- **Age (in Years):** We divided population into three groups according to age, those less than 45 years, those between 45 and 59, and lastly those who are 60 years or more.
- **Hypertension:** Patients were classified as hypertensive if they have a history of hypertension under treatment (35)
- **Diabetes Mellitus:** Diabetes has been classified by simply history, by the use of insulin or other hypoglycemic agents or by fasting blood sugar more than 126mg/dl (36).
- Hyperlipidemia once considered to be present if total cholesterol greater than 200mg/dl or serum triglyceride greater than 250mg/dl or both (37).
- **Smoking:** Was considered present if the patient currently smokes 10 cigarettes per day or more (38).
- **Family History of CAD:** This variable should be defined as having a cardiac event (infarction, angioplasty, bypass, sudden in a first degree relative under the age of 55 years for men and 65 years for women (35).
- **Ejection Fraction:** A value less than 50% is considered to be abnormal (25) 5
- Left ventricle end diastolic pressure is considered abnormal if more than or equal to 15mm Hg.
- Past history of MI as documented by E.C.G. and previous admission to CCU. Tab 1

STATISTICAL ANALYSIS

Analysis of covariance (ANOVA) and multiple linear regressions using Gensini score as dependent variable was also Performed for testing the statically significant difference between coronary risk & Gensini severity Score. P- value less than 0.05 considered to be significant.

THE RESULTS

Description of the Study Sample

The highest proportion of the study sample (55.1%) were in the middle age group (45-59) years, Elderly females constituted (29.1%) of the study sample.

A positive past history of MI was elicited in (29.5%) of the sample, about two thirds of females (62%) had recurrent CCU admission. About one third (35.3%) of patients had hypertension, (19.2%) had diabetes. The majority (85.1%) were non-smokers, and family history of IHD was elicited in (20.7%) of cases. Regarding hyperlipidemia; about 40% of patient had serum cholesterol more than 200mg/dl. About 42% have impaired ejection fraction with high left ventricular end diastolic pressure. See also table 1.

The Prevalence of Coronary Artery Disease as Shown by Angiogram

CAD considered to be present if the luminal narrowing of the involved artery more than 50% of the left main stem, or more than 70% in other arteries. As shown in figure 1, nearly 58% of cases have normal coronary arteries. Of those who have diseased coronaries, about half have single artery involved, while two arteries and three arteries constituted the remaining half see figure 2.

Assessment of CAD Severity by Angiography

The angiograms of about 58% of cases showed none of the coronaries involved and constituted zero score. Those with mild involvement (a score of 1-29) constituted 11% moderate involvement (a score of 30-59) constituted 17.8%. figure 3

The Association between Certain Variable and Angiographic Severity

These associations will be studied first by univariate analysis, then by multivariate analysis assuming that the association between each risk factor and gensini score is Independent of the effect of the rest. As shown in table 1 the most important variables which correlated with the severe involvement was diabetes and smoking, other variables like past history of MI, hyperlipidemia, age, low ejection fraction and elevated LVEDP also show significant involvement. While family history of IHD and hypertension were not significantly associated with severity of coronary involvement.

As shown in table 2, the multiple regression model shown statistically significant these are: being a smoker, diabetic, having hyperlipidemia, hypertensive, having ejection fraction less than 45%, increased LVEDP, being elderly, and having past history of MI.

Being a diabetic increasing the risk of developing positive coronary involvement six fold, past history of MI by about five fold (4.9), in addition being smoker increase the risk by four time (4.1), and it doubles the risk when having high LVEDP, the same results were in hyperlipidemic patient and those having low ejection fraction. Being elderly more than 60 years increase the risk by about 3.7 times than those who were less than 45 years old. In contrast the risk was not increased in those who are hypertensive.

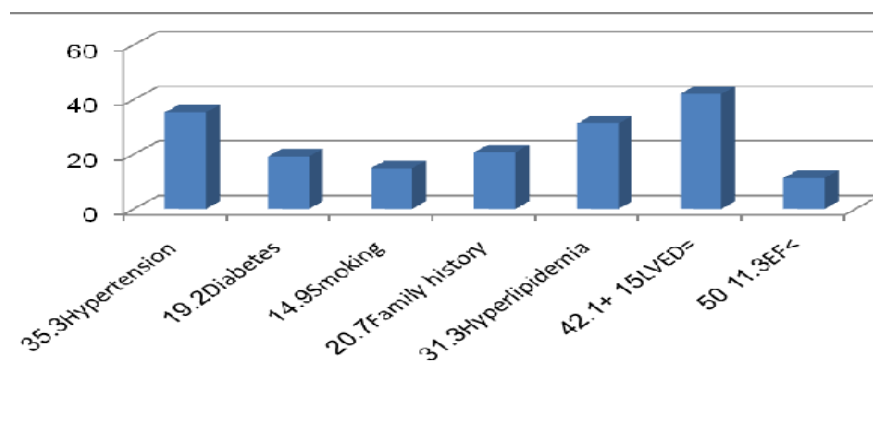


Table1: Prevalence of Certain Variables among Study Sample

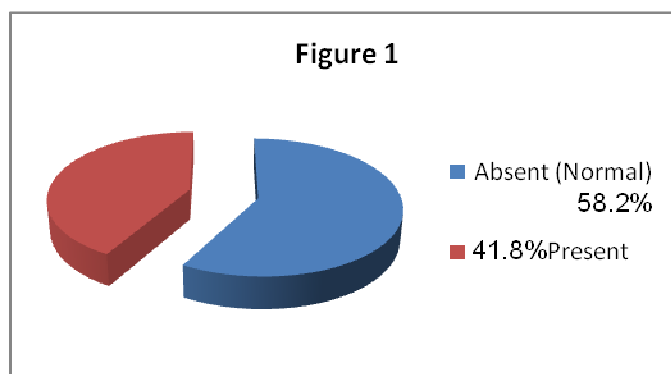


Figure 1: Shows the Ratio of Normal to Abnormal Coronary Angiography

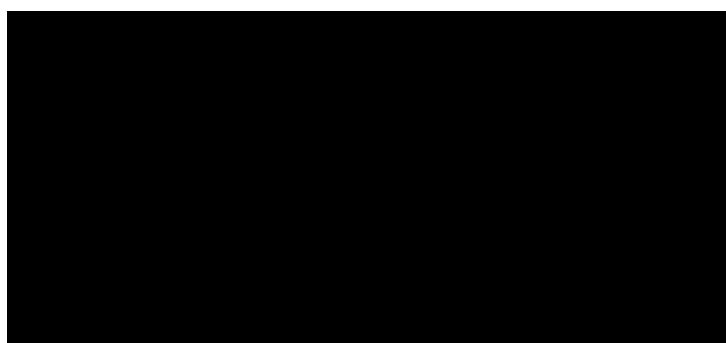


Figure 2: Pie Chart Showing the Distribution of Angiogram Positive Patients by Number of Blood Vessel Involved

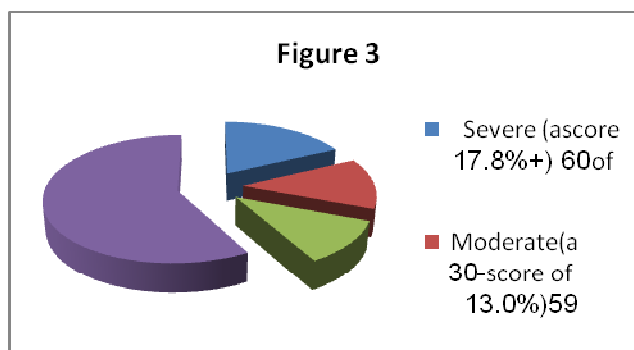


Figure 3: Pie Chart Showing the Distribution of the Study Sample by IHD Severity

Table 2: A Multiple Logistic Regression Model with the Risk of Having a Positive Angiogram for Coronary Arteries Involvement as the Dependent Variable Model P Value, 0.001 Predictive Power for a Positive Angiogram

Dependant Variable	OR	P Value
Age in yrs compared to <45 yrs old group		0.02
45-59	2.4	
60+	3.7	
High LVEDP (15+) compared to low (<15)	2	0.01
A low EF <50 compared to a normal one 50+	2	0.01
Being a hypertensive	0.9	0.72
Being a diabetic	6	0.001
Being a smoker	4.1	<0.001
Having a hyperlipidemia	2	0.01
Positive history of MI	4.9	<0.001

DISCUSSIONS

The study focused on the angiographic extent and severity of coronary atherosclerosis and its relation to well known risk factors like diabetes, smoking, hypertension, hyperlipidemia and family history of ischemic heart disease, in addition to certain variables like past history of MI, LVEF and ejection fraction.

Diabetes was the most powerful risk factor that correlates with severity and extent of coronary atherosclerosis. This correlation was statistically significant even after controlling for other risk factors using multiple linear regression analysis, so being diabetic women has a six fold to have coronary artery disease proved by angiogram study. This was in agreement with Muscat et al and kip et al who reported that, diabetes is associated with a threefold to sevenfold elevation in CHD risk among women, compared with a twofold to threefold elevation among men (39, 40)

The second most important parameter is past history of myocardial infarction, women with past history of myocardial infarction have nearly fivefold of having a positive coronary angiogram as compared with negative past history of MI presented with angina symptoms. This was in agreement with Bemis et al who found that progression in 52% of 73 coronary patients who were reconsidered after an average interval of 23.8 months of myocardial infarction (42). In 200 patients with ischemic heart disease, Kramer et al reported progression at an interval of 36.5 month in 65% of those who had interim infarction compared with 44% among those who had not.(43)

The third most important factor was smoking. Being a smoker woman increases the risk of having a positive coronary angiogram by about four times women who are not smoker. Hays JT et al proposed that the magnitude of excess risk of coronary artery disease is twofold to fourfold elevation, is similar in women and men. Waters et al and Gottlieb et al demonstrates that coronary atherosclerosis progresses much more rapidly in smokers than in nonsmokers. The rate of progression, a mean narrowing of minimal lumen diameter of all coronary lesions by 0.16 mm in 2 years in placebo-treated smokers, was more than double the rate of 0.07 mm in placebo-treated nonsmokers. Furthermore, new lesions developed in more than half Kugiyama et al. Cigarette smoking is a major risk factor for coronary artery disease and is highly prevalent in patients with coronary spastic angina. Nitric oxide bioactivity at rest and at acetylcholine-stimulated condition in smokers was decreased, leading to the super sensitivity of the artery to the dilator effect of nitroglycerin as well as the constrictor effect of acetylcholine in smokers (47, 48).

Dysfunction of vascular endothelium and an abnormal interaction with blood monocytes and platelets lead to subintimal collection of abnormal fat, cells, and debris (i.e., atherosclerotic plaques), which develop at irregular rates in different segments of the epicardial coronary tree and lead eventually to segmental reductions in cross-sectional area (41).

It might be proposed that the rate of progress as a consequence of the destabilization process varies according to "maturation" stage in the life of an atheroma cycle. In most growing lesions, progression is probably rapid, and its maximal expression is at the level of the offending plaque; acute

Progression of non-offending plaques persists or regresses according to the persistence of the inciting process, occurrence of shrinkage, mural thrombus lyses, or vascular remodeling. The fact of the culprit lesion is in part related to thrombus. Taken together, these results are consistent with the hypothesis that acute infarction of the heart is a hallmark of a systemic progression involving multiple coronary artery plaques and is not purely a reflection of increased atherosclerotic activity in a single plaque (44-50)

our result in agreement with national studies like Hadi et al also found that smoking and a history of diabetes were more prevalent in patients with three vessel diseases than those with single vessel and double vessel diseases (54). The other important risk factor that correlated with angiographic severity was the age, without the contribution of the other risk factors it increase the risk by two to three fold as compared with those less than 45 years old, Grundy et al reported that absolute risk for CHD increases with age in both men and women as the result of progressive accumulation of coronary atherosclerosis with aging. In fact, most new-onset CHD now occurs after age 65; this trend is especially pronounced in women because of a high absolute risk in elderly patients, opportunities for primary prevention in this age group should be substantial (49).

Hyperlipidemia is another important risk factor; we found that women with hyperlipidemia have a higher index of severity score as compared to those with normal lipid level. This was also significant also after controlling other factor by multivariate analysis. A woman with hyperlipidemia has double the risk of developing CAD as compare to those with normal levels. This is in agreement with French et al who studied 488 patients with CAD angiographically; found that the severity of disease had statistically significant positive correlation with the level of total cholesterol (51). Sharp et al also reported that the mean angiographic severity score were significantly higher among patients with familial hypercholesterolemia (52). It has been proposed that cholesterol (especially modified LDL) is a major cause of injury to endothelial and smooth muscle cell and act as a mutagen leading to intimal and smooth muscle cell proliferation. In addition modified LDL is a chemotactic for other monocytes and can up regulate the expression of genes for macrophage colony stimulating factor and monocytes chemotactic protein. Thus it may help to expand inflammatory responses which inter have profound effect on lipoprotein movement within the artery and progression of atheroma (10). This could explain the association of hyperlipidemia with severe CAD.

In this study we have found a significant relation between elevated left ventricle end diastolic pressure and low ejection fraction if taken as an index for LV function and coronary artery disease. we have found that those with elevated LVEDP and low ejection fraction, have double the risk to develop significant CAD as shown by the abnormal coronary angiogram. Booth et al reported that LVEDP-associated with coronary artery disease possibly due to high microvascular resistant to the coronary blood flow (50). Other possible explanation is made by Gheorghiade and Bonow that release of endothelin is increased in failing myocardium and that angiotensin promotes the release of endothelin and the excessive degradation of nitric oxide). These observations suggest an interplay between the failing myocardium and the coronary endothelium that potentiates the progression of both CAD and LV dysfunction (54-55). This was also in agreement with Cheitlin et al who reported that finding of low ejection fraction predict the presence of ischaemic heart disease (56).

Framingham data considers a positive family history of premature CHD a risk factor and uses it in defining risk status. However, the independent effect of a positive family history is difficult to determine. Almost certainly familial influences on risk status are mediated in part through blood

Pressure and serum lipoprotein levels. Even so, a positive family history of premature CHD cannot be ignored in clinical evaluation. Not only should such a history increase awareness that an individual is at greater risk, but it calls for evaluation of other family members who may carry heritable risk factors (56).

CONCLUSIONS

- Normal coronary angiography is present in 58% of women presented with chest pain, and of those who have abnormal coronaries about half of them have single vessel involved (most commonly left anterior descending artery).
- Diabetes mellitus is the single most important risk factor of coronary artery disease; those women have six fold have the risk as compared with non-diabetic.
- CAD is a disease of post-menopausal women.
- Past history of MI. raises the risk to develop CAD five times the risk to develop CAD.
- Smoking raises the risk to develop CAD four times than those who were notsmokers. 6. Left ventricular systolic dysfunction as reflected by low ejection fraction and elevatedLVEDP is an important association correlated with severe CAD.
- Hyperlipidemia correlates significantly with severe CA.
- Hypertension was not correlated with severe CAD

RECOMMENDATIONS

Since most of female patient which was referred for coronary angiography were normal, the threshold for invasive test as coronary angiography need to be raised in female patient. Although early referral for those how had diabetes, smoker or with previous history of ischemic heart disease or being elderly or with positive family history of ischemic heart diseases.

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